Reversibility of Ischemia Evaluated by Ischemic Duration and Residual Cerebral Blood Flow

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Summary

We first investigated the time course of CBF thresholds of ischemic cortices by a retrospective review of 19 patients with MCA occlusion who had clearly defined ischemic duration from onset to angiographic complete recanalization. Secondly, CBF thresholds of ischemic cortices salvageable with intravenous low dose native t-PA infusion therapy (7.2 mg of tisokinase) were examined by a retrospective review of 20 patients with distal embolic occlusions of MCA divisions or branches. All patients underwent pretreatment CBF measurement by SPECT using 99mTc-ECD. Pretreatment SPECT and 3 months post-treatment CT images were compared using computerized coregistration. The degree of hypoperfusion was analyzed by an asymmetry index (AI), which was a count-density ratio for the ischemic lesion to the contralateral corresponding area. Ischemic cortices on SPECT were divided into reversible and irreversible lesions.

Judging from the regression lines with 95% confidence interval between the ischemic duration and AI, the infarcted CBF thresholds at 3 and 6 hours after onset may be about 30 and 50 % of contralateral presumed normal CBF, respectively.

On the other hand, to save the ischemic tissue with our intravenous t-PA infusion therapy, residual CBF might be needed at least 45 % of contralateral presumed normal CBF. It is likely that CBF threshold of ischemia surely salvageable with our intravenous t-PA infusion therapy may be approximately 50-55 % of contralateral presumed normal CBF.

Introduction

It is very important for patient selection in reperfusion therapies to evaluate reversibility of ischemia. In most therapeutic trials of thrombolysis, however, patient selection was performed mainly by ischemic duration and very early treatment within 3-6 hours has been emphasized [1-4]. To be sure, ischemic duration is an important prognostic factor for thrombolytic therapy. However, a fixed 3 or 6 hours therapeutic time window for acute stroke therapy does not correspond to the individual pathophysiological state [5]. The European Cooperative Acute Stroke Study (ECASS) II results [6] indicate that intravenous alteplase might not lead to a clinically relevant improvement in outcome when the patient selection was performed based on the ischemic duration alone. Apart from ischemic duration, another important factor contributing to the reversibility of ischemia may be the severity of ischemia. When the residual cerebral blood flow (CBF) is reduced markedly, even very early recanalization might result in unfavorable outcome. On the other hand, when the residual CBF is well preserved, there is no need to stick to a rigid therapeutic time window within 3-6 hours. Not only ischemic duration but also residual CBF in the

ischemic territory should be taken into consideration to evaluate reversibility of ischemia. On the basis of these considerations, we first investigated the time course of the CBF thresholds of ischemic cortices.

Secondly, we investigated the CBF thresholds of ischemic cortices salvageable with intravenous t-PA infusion therapy.

Subject and Methods

Sixty-five patients with acute middle cerebral artery (MCA) occlusion were treated by some reperfusion therapy over the past 6 hours. Inclusion criteria for reperfusion therapy consisted of the presence of major arterial occlusion consistent with clinical symptoms; absence of apparent hypodensity on the initial computed tomography (CT) related to the ischemic events; and availability of informed consent from the patient or a family member. Our methods of reperfusion therapy have been previously reported [7]. Briefly, direct percutaneous transluminal angioplasty (PTA) was performed in patients with M1 trunk occlusions with involvement of the lenticulostriate arteries (LSAs). Angioplasty was performed with a Stealth angioplasty balloon catheter (Boston Scientific, Quincy, MA, USA) with maximum diameter of 2.0 to 2.5 mm. In case of partial recanalization by direct PTA, subsequent intravenous or intra-arterial thrombolytic therapy was performed using tissue plasminogen activator (t-PA). Local intra-arterial thrombolysis was performed in patients with M1 trunk or more distal occlusions without LSAs involvement. Since 1996, intravenous t-PA infusion was selected as the first choice of the treatment in patients with occlusions of MCA divisions or branches with well opacified LSAs [8].

Among these 65 patients, 19 had a clearly defined ischemic duration from onset to complete recanalization confirmed by intra-therapeutic angiography and were selected for the first study. In these 19 patients, direct PTA and / or intra-arterial thrombolysis were performed. The time from symptom onset to reperfusion ranged from 2.5 to 8.0 hours (average, 4.1 hours). On the other hand, 20 patients were selected for the second study with intravenous thrombolytic therapy using 7.2 mg of native t-PA (tisokinase, Asahi Chemical Industry Co., Ltd., Japan). All patients in both studies underwent pretreatment CBF measurement by single photon emission CT (SPECT) using 99mTc-N, N'-(1,2-ethylenediyl) bis-L-cystein diethylester (99mTc-ECD).

99m Tc-ECD was injected just before reperfusion therapy and SPECT scanning was performed just after treatment. SPECT scans were performed using a dual headed gamma camera system (OPTIMA, GE-YMS, Tokyo, Japan) with high resolution collimators (FWHM=11 mm). SPECT acquisition was performed in 64 steps, 360° and with a 128 x 128 matrix. Transaxial images were reconstructed by filtered backprojection using both Butterworth and ramp filters with attenuation correction. Lassen's linearization correction algorithm for 99mTc-hexamethyl-propyleneamine oxime (99mTc-HMPAO) was applied for backdiffusion correction. The ipsilateral CBF change was estimated by asymmetry index (AI). AI was calculated as Ca/Cb x 100%, where Ca is the mean reconstructed counts for the ipsilateral ischemic area and Cb is the mean reconstructed counts for the contralateral corresponding area.

Follow-up CT scan was obtained 3 months after onset. For the retrospective analysis, pretreatment SPECT and follow-up CT images were compared using computerized coregistration and ischemic cortices on SPECT were divided into reversible and irreversible ischemia. Regions of interest (ROIs) were placed on the cerebral cortices (20 x 20 mm, square) in the MCA territory.

Hypoperfusion cortices on pretreatment SPECT images were classified into two groups: 20 irreversible lesions fell into cerebral infarctions on the follow-up CT scan in 7 patients and 107 reversible lesions escaped from cerebral infarctions in 19 patients in the first study, and 25 irreversible lesions in 9 patients and 38 reversible lesions in 20 patients in the second study, respectively. AIs were calculated in the reversible lesions and irreversible low density areas on the follow-up CT scans. In all patients, recanalization was confirmed by follow-up angiography or MR angiography.

In the first study, correlation of the ischemic duration and AI was assessed using a linear regression analysis with commercially available software (StatView 4.5 J; Abacus Concepts, Berkeley, CA). In the second study, the statistical analysis was performed using Mann-Whitney U test.

Results

Regression lines between the ischemic duration and AI in reversible and irreversible lesions are shown in figure 1. The ischemic tissue below the line expressed as the upper limit of 95% confidence interval (CI) of irreversible lesions fell into infarct in spite of reperfusion. This line may be substituted for a time-threshold curve. On this line, AIs at 3 and 6 hours after onset were about 30 and 50%, respectively. On the contrary, the ischemic tissue above the line expressed as the lower limit of 95% CI of reversible lesions was certainly salvageable by reperfusion. This line may be substituted for another time-threshold curve. On this line, AIs at 3 and 6 hours after onset were about 55 and 65%, respectively.

In the second study, AIs in the 25 irreversible lesions ranged from 15.0 to 53.4% (37.3 ± 11.6%), whereas AIs in the 38 reversible lesions ranged from 45.0 to 83.1% (69.3 ± 8.6%). There was a significant difference of AIs between these two groups ($p<0.0001$). The ischemic tissue with AI greater than 53.4% was reversible. On the contrary, the ischemic tissue with AI less than 45.0% could not escape from cerebral infarction with our treatment. The ischemic tissue with AI between 45.0 and 53.4% was reversible in some patients and irreversible in others (figure 2).

Discussion

Though the ischemic thresholds may change with time [9,10] and the development of infarction is too complex to be described by a single threshold concept [11,12], determining a certain measure of standard critical CBF may be useful for the management of acute ischemic stroke. In our previous study using N-isopropyl-p-[123I]-iodoamphetamine (123I-IMP) SPECT [13], infarcted and symptomatic CBF thresholds were 39-48 and 65-72% of contralateral presumed normal CBF, respectively. The ischemic tissue with CBF between these two thresholds may be the best candidate for reperfusion therapy.

Our present study has demonstrated that the ischemic tissue below the line expressed as the upper limit of 95% confidence interval (CI) of irreversible lesions fell into infarct in spite of reperfusion. When this line is substituted for a time-threshold curve, infarcted flow thresholds

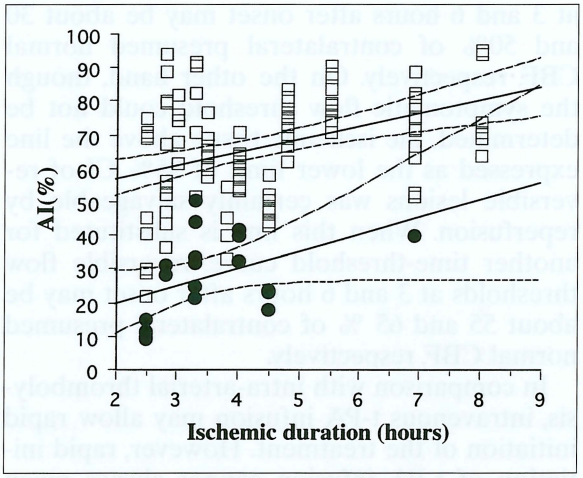

Figure 1 Reversibility of ischemia versus severity and duration of ischemia. The line expressed as the upper limit of 95% confidence interval (CI) of irreversible lesions (●) may be substituted for a time-threshold curve. The infarcted flow thresholds at 3 and 6 hours after onset may be about 30 and 50% of contralateral presumed normal CBF, respectively. On the other hand, the line expressed as the lower limit of 95% CI of reversible lesions (□) may be substituted for another time-threshold curve. The reversible flow thresholds at 3 and 6 hours after onset may be about 55 and 65% of contralateral presumed normal CBF, respectively.

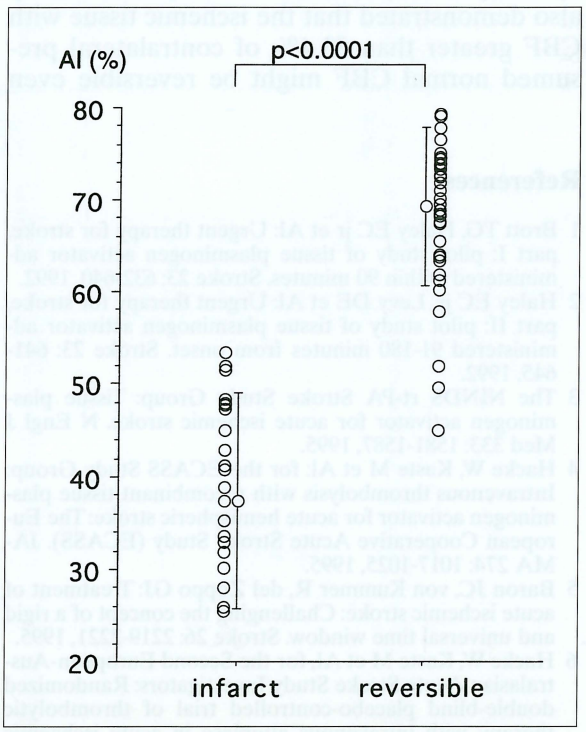

Figure 2 Ischemic degree of reversible and irreversible lesions. Asymmetry indexes (AIs) in the irreversible lesions ranged from 15.0 to 53.4% (infarct, 37.3 ± 11.6%), whereas AIs in the reversible lesions ranged from 45.0 to 83.1% (reversible, 69.3 ± 8.6%). There was a significant difference of AIs between these two groups ($p<0.0001$).

at 3 and 6 hours after onset may be about 30 and 50% of contralateral presumed normal CBF, respectively. On the other hand, though the symptomatic flow threshold could not be determined, the ischemic tissue above the line expressed as the lower limit of 95% CI of reversible lesions was certainly salvageable by reperfusion. When this line is substituted for another time-threshold curve, reversible flow thresholds at 3 and 6 hours after onset may be about 55 and 65 % of contralateral presumed normal CBF, respectively.

In comparison with intra-arterial thrombolysis, intravenous t-PA infusion may allow rapid initiation of the treatment. However, rapid initiation of t-PA infusion cannot always mean rapid recanalization. Since intravenous t-PA infusion therapy may have a chance of delayed recanalization, it may be desirable for successful treatment to select patients with sufficient residual CBF above the infarcted threshold. In the 99mTc-HMPAO SPECT study by Ueda et Al [14], ischemic tissue with CBF greater than 55% of cerebellar flow may be reversible even by delayed recanalization. Our present study also demonstrated that the ischemic tissue with CBF greater than 53.4% of contralateral presumed normal CBF might be reversible even by our intravenous t-PA infusion therapy. On the contrary, the ischemic tissue with CBF less than 45.0% of contralateral presumed normal CBF could not escape from cerebral infarction with our treatment. The ischemic tissue with CBF between 45.0 and 53.4% of contralateral presumed normal CBF might be salvageable by early recanalization and might become irreversible when recanalization were delayed.

Conclusions

From these results, pretreatment CBF SPECT is feasible for patient selection in reperfusion therapies for acute ischemic stroke. To save the ischemic tissue with a prompt and reliable recanalization therapy, residual CBF might be needed at least 30 or 50% of contralateral presumed normal CBF at 3 or 6 hours after onset, respectively. On the other hand, to save the ischemic tissue with our intravenous t-PA infusion therapy, residual CBF might be needed at least 45% of contralateral presumed normal CBF. It is likely that CBF threshold of ischemia surely salvageable with our intravenous t-PA infusion therapy may be approximately 50-55% of contralateral presumed normal CBF.

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